Estimate of incidence of ROP requiring treatment in extreme preterms and impact on service – 7 year review in tertiary unit

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Abstract:

Background/Objectives

Retinopathy of prematurity (ROP) is a potentially blinding disorder affecting premature infants. Our Eye Unit supports 2 neonatal intensive care units (NICUs), one provides neonatal surgical and medical facilities and the other is exclusively medical. Our objectives were to (1) to identify the annual rate of ROP treatments during the period 2009-2015 and (2) to estimate the incidence of ROP treatment in babies born very prematurely (<27 weeks).

Subjects/Methods

Records for all infants treated for ROP by our unit during the period 2009-2015 were reviewed. We calculated numbers treated in each year. Records of babies born under 27 weeks of gestation and cared for in the non-surgical NICU were also reviewed. Their requirement for laser treatments for ROP was calculated by week of gestation at birth.

Results

In the 2 NICUs combined, 95 infants were treated for ROP between 2009 and 2015. The numbers treated increased from 9/158 (5.7%) of babies screened in 2009 to 22/159 (13.8%) in 2015 (p_{trend} 0.004). The rate of laser treatment for ROP increased as gestation at birth decreased: from 12/100 (12%) of babies born at 26 weeks to 17/29 (59%) of babies born at 23 weeks (p_{trend} =0.001).

Conclusion

The number of laser treatments for ROP carried out by this unit has increased steadily between 2009 and 2015 and may in part be due to the increased need for ROP treatment in extremely preterm babies, whose survival has increased in the same period. This data may aid planning for ROP services.

Introduction:

Retinopathy of prematurity (ROP) is a potentially blinding disorder affecting premature infants. Risk factors include a low gestational age and a low birth weight[1]. ROP is a major cause of preventable blindness in children worldwide[2]. The proportion of blind children affected by ROP has been reported as 37.4% in Former Soviet Economies and 23.9% in Latin American countries, in contrast with 10% in established market economies such as the UK and nil or extremely rare in sub-Saharan Africa[1]. The reasons for these differences are thought to include variation in levels of training in neonatal care and the ability to monitor oxygen saturations in babies having supplemental oxygen and the availability of ophthalmic support for screening and treatment.

Guidelines exist for screening to identify sight-threatening stages of ROP and to instigate timely treatment. Screening and treatment for ROP in the UK follows the guidelines set jointly by The Royal College of Ophthalmologists and the Royal College of Paediatrics and Child Health[3]. These use the nomenclature and descriptions (location in retinal zones 1-3; severity in stages 1-5 and plus or pre-plus to describe increases in retinal vessel calibre and tortuosity) of the International Committee for the Classification of ROP[4]. The current criteria for treatment are based on the Early Treatment of Retinopathy of Prematurity Study (ETROP)[5]. The features of ROP requiring treatment are collectively known as "Type 1 ROP" which includes any stage ROP in zone 1 with Plus; Zone 1 stage 3 with or without plus; zone 2 stage 2 or 3 ROP with plus. Treatment may also be given for "Type 2 ROP" if there is clinical concern, otherwise this can be kept under review until progression to type 1 ROP or regression takes place.

Screening in the UK is currently recommended for all babies born at less than 32 weeks gestation or weighing less than 1501 grams, starting at 4-5 weeks after birth or 30 weeks gestation (whichever is the later) and should continue until the retina is fully vascularised, or treatment is required. A recent national prospective surveillance study in the UK reported the incidence of ROP requiring treatment to be 4% in infants with birth weight <1500g[6], which is greater than previous estimates of 1.5-2%[7,8]. This study reported the majority of primary treatments for ROP were by diode laser photoablation of the avascular retina in 90.5% of babies and intravitreal injection of an anti-VEGF (currently not licensed) in 8%[6].

In our Eye Hospital unit we treat babies with ROP cared for in either of two local level 3 neonatal intensive care units (NICUs) and some babies from other NICUs as requested. One of our NICUs offers regional surgical and medical facilities for neonates, whilst the other is exclusively medical and cares for a higher proportion of the extreme premature infants.

We had noticed an increase in the numbers of laser treatments being performed over the last few years and aimed to review this to inform future capacity planning. Additionally, as international studies have reported increased incidence of treatment-requiring ROP in very prematurely-born babies as compared with babies born at higher gestations[9,10,11,12], we aimed to determine whether this was the case for our UK-born neonates.

The aims of this study were therefore twofold: firstly, describe yearly ROP treatments during the 7-year study period (2009 to 2015) and secondly to estimate the rates of

ROP requiring treatment in infants born very preterm (<27 weeks), by weekly category of gestational age.

Patients and methods:

First aim: laser treatments carried out per year by our unit

For the first aim we retrospectively reviewed the clinical data of all the infants that were treated for ROP by the Vitreoretinal (VR) team at Bristol Eye Hospital between 1 January 2009 to 31 December 2015. Babies screened for ROP in Bristol include Bristol-booked infants and babies transferred to Bristol for tertiary care. Of note, the referral pathways did not change over the time period studied. The Western Network and Peninsula Network (lead centre Plymouth) combined in January 2013 to form the South West Neonatal Network but this did not change the referral pathways for the tertiary units in the Network so Bristol did not receive referrals from a wider area at any time during the study.

For all babies we used the recommended criteria for screening (birth weight <1500g and/or <32 weeks gestation) and the first examination was at 4-5 weeks after birth or 30 weeks gestation, whichever was the later. Examinations were carried out weekly. Treatment decisions were based on the 2008 RCOphthal ROP Guidelines[3]. Initial treatment for all subjects consisted of transpupillary indirect ophthalmoscope diode laser therapy of laser burns to the entire avascular retina. Review was undertaken within 5-7 days, then weekly after treatment and the decision for further treatment (with either an intravitreal anti VEGF agent, further laser or vitrectomy) was taken 2-3 weeks later if regression was not evident.

Infants that had been treated for ROP during the study period were retrospectively identified from a laser book held at the Eye Hospital and cross-referenced against lists held by the individual neonatal units identifying the individuals that were treated. Clinical data was taken from the neonatal electronic patient record database Badger Net.

Second aim: rates of ROP needing treatment by gestational age at birth

For the second aim, we reviewed the notes and database records of all babies under 27 weeks cared for in the exclusively medical NICU. Care of babies under 27 weeks in the Western neonatal network is centralised to NICUs in our area, the majority in the exclusively medical NICU. In order to estimate the survival rates and the need for laser treatment in extremely premature infants, we used as denominator all infants who were born or transferred within 48 hours of birth to the exclusively medical NICU. For those who were transferred out of our area before their ROP screening was completed we checked the national or regional neonatal database for details of any laser treatments carried out elsewhere.

Therefore the groups of babies used to answer each question are not the same, although there is overlap between them. Statistical significance was assessed with extended Mantel-Haenszel chi square for linear trend.

Results:

Study Aim 1: Laser treatments carried out each year between 2009 and 2015

During the 7-year study period, a total of 95 infants were treated for ROP, by the local vitreoretinal team (table 1). Laser treatments were carried out under sedation and muscle relaxant, with intubation to support their ventilation. Each NICU had a dedicated room for the purpose and provided full nursing and neonatology support.

Total infants	95
Gender Male Female	 48 (50.5%) 47 (49.5%)
Maternal steroids	87%
Birth weight (mean±SD)	699.9 ± 160.7g
Gestation (mean ± SD)	24 weeks ± 1.3 weeks
Age at which treatment was undertaken (mean±SD)	90.6 ± 45.7 days

Table 1: Details of the 95 infants treated for ROP by the VR consultants at Bristol Eye Hospital between 2009-2015.

Over the time period studied (2009-2015) 8.2% of the infants who were examined, required treatment for ROP. There was a year-on-year increase in the absolute number treated with significantly more treated in 2015 compared to 2009 (Table 2). In the majority of cases (82 of 95, 86%) treatment consisted of one course of laser treatment alone. Additional treatment following the first course of laser was required in the remainder (13 of 95, 14%). This consisted of two courses of laser in 5 of 95 (5.3%), laser followed by an intravitreal injection of anti vascular endothelial growth factor (VEGF) in 7 of 95 (7.4%) and laser followed by vitrectomy in 1 of 95 (1.1%), in this case the infant was referred to a different centre for the vitrectomy due to aggressive ROP failing to regress following the initial laser treatment.

Of these 95 babies, approximately two thirds were not later resident in Bristol, but were transferred to other units near their homes.

Year	Numbers of babies treated	Numbers of babies examined in the two NICU units combined	Percentage of examined babies treated
2009	9	158	5.7%
2010	9	169	5.3%
2011	12	177	6.8%
2012	16	162	9.3%
2013	11	162	6.8%
2014	16	165	9.7%
2015	22	159	13.8%
Totals	95	1152	8.2%

Table 2: ROP treated infants as a percentage of those screened each year. A significantly greater percentage of infants were treated each year following a linear trend. Extended MH Chi Sq = 8.24, df=1, p=0.004.

Study Aim 2: Incidence of ROP treatment by gestational age

Over the time period studied (2009-2015) 333 infants <27 weeks were cared for at the exclusively medical NICU. Of these 269 (81%) survived to complete ROP screening (table 3). Figure 1 shows the number of babies <27 weeks gestation cared for at the exclusively medical NICU and the number surviving to complete ROP screening increased from 2009 to 2015. Their survival improved from 69% in 2009 to 90% in 2015.

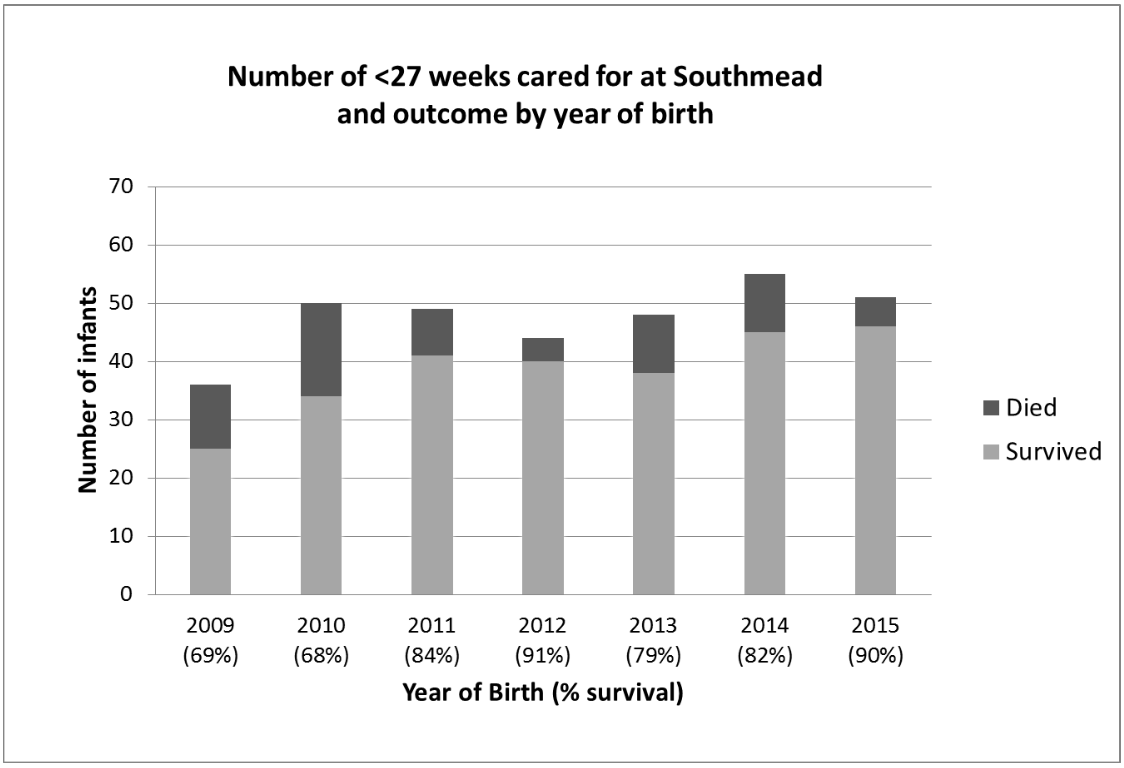

Figure 1: The number of <27 weeks gestation babies cared for and survived to complete ROP screening by year of birth.

Survival to complete ROP screening improved with increasing gestation; 69% of 23 week gestation and 88% of 26 week gestation infants survived (table 3). ROP treatment was required for 69 of 269 (26%) of extremely premature babies that survived to complete ROP screening. Of these 56 (81%) were treated in Bristol (and are included in the first study aim) and 13 (19%) were treated at their base unit. The incidence of ROP treatment increased in proportion with the degree of prematurity at birth: extended MH chi sq for linear trend =28.57; df=1; p <0.001. As shown in Figure 2, 17/29 (59%) of those born at 23 weeks gestation required treatment compared to 12/100 (12%) of those born at 26 weeks gestation (Figure 2).

Table 3. Outcome for those <27 weeks cared for at Southmead

Gestation (weeks+days)	23+0 to 23+6	24+0 to 24+6	25+0 to 25+6	26+0 to 26+6	23+0 to 26+6
Number	42	74	104	113	333
Survived to complete ROP screening (%)	29 (69%)	58 (78%)	82 (79%)	100 (88%)	269 (81%)
Survivors treated for ROP (%)	17 (59%)	22 (38%)	18 (22%)	12 (12%)	69 (26%)
Survival without ROP (%)	12 (29%)	36 (49%)	64 (62%)	88 (78%)	200 (60%)

Died + ROP treatment (%)	30 (71%)	38 (51%)	40 (38%)	25 (22%)	133 (40%)

Table 3: Numbers care for and percentage survival to complete ROP screening for each week of gestation.

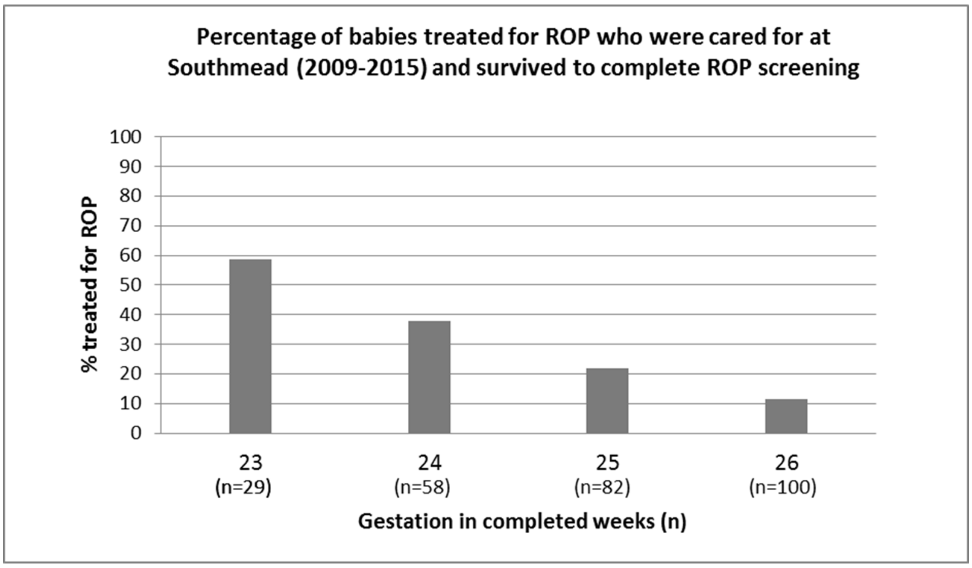

Figure 2: Incidence of ROP treatment by gestational age at birth.

Discussion:

We aimed to answer two questions: firstly, was our unit carrying out increasing numbers of laser treatments for ROP over the last few years and secondly, in a cohort of extremely premature infants, did the rates of ROP needing treatment vary by week of gestational age at birth. We found that the absolute numbers of laser treatments carried out had increased, with no increase in the overall numbers of babies examined each year, suggesting the babies in our local units were increasingly higher-risk (for ROP) as the study period progressed. We also observed that in a cohort of extremely premature (<27 weeks at birth) infants, not only were they increasingly more likely to survive as the study period progressed, but also the rate of ROP requiring treatment varied inversely with their gestational age at birth. Thus whilst 12% of babies born at 26 weeks and survived needed laser for ROP, this was nearly fivefold higher for babies born at 23 weeks and survived (table 3). These data suggest that the increase in ROP treatments we have carried out during the study period is in part be due to the increased survival of the more extreme premature infants. A recent population-based study showed the survival to discharge of extreme preterms in England between 2008-2014 was 36% for 23 weeks gestation, 59% for 24 weeks, 74% for 25 weeks and 83% for 26 weeks[13]. These survival rates are lower than those we observed in this study especially for the lower gestations (69% for 23 weeks gestation and 78% for 24 weeks). Thus a small improvement in survival of the more extremely premature babies especially those at 23 and 24 weeks gestation will have a greater impact on the numbers requiring ROP treatment and therefore the ophthalmology service. Since 2008, in the UK as a whole, all care for <27 weeks gestation infants has been centralised to tertiary neonatal units such as the two in our city. This centralisation of services also increases the demands on the reduced numbers of Eye units carrying out ROP treatments and is a likely additional reason for the increase in ROP treatments we have observed.

Our study is not a population-based study and therefore cannot be used to estimate incidence of ROP treatment of those eligible for screening (<1500g and/or <32 weeks gestation). The babies examined in the two NICUs include Bristol-booked infants and those born <27 weeks from the wider regional neonatal network, but excludes prematurely-born local babies cared for in nearby level 2 centres. Previous studies have reported incidence of ROP treatment is increasing[14] and the recent national surveillance study found that more babies were treated for ROP in 2014 than were reported in a previous national study[15]. In our study all babies were treated by diode laser as a primary treatment and 13.7% (13/95) required further treatment. This is similar to the national picture[6]. The use of other forms of treatment such as anti VEGF intravitreal injections remains off licence in the UK, and this is an area where further research is required, particularly in identifying the safety profile of these medications systemically in premature infants. In our study, an anti VEGF intravitreal injection was used as a second-line agent in 7 of the 13 cases where initial treatment had failed to result in resolution of the ROP. In the recent national audit 8% of babies received anti-VEGF as firstline treatment[6]. Other reports have suggested that anti VEGF intravitreal injections, may be of value in cases where there is poor visibility of the retina, which would make laser treatment difficult, or in cases where laser treatment has failed to result in regression of ROP[16].

A limitation of our study is that we have considered just one geographic area and the results may not be generalizable to other areas. The recording of ROP laser treatments in the laser book and/or the neonatal database may have been inaccurate and we could not cross-check data sources for babies treated outside our unit. We did not record stage of ROP triggering the decision to treat, so the threshold for treatment may have varied over the study period and there is also well-recognised variability between ophthalmologists for example regarding presence or absence of Plus disease[17]. However the same team were involved in screening and treatment throughout the period and national guidelines did not change. A strength of this study is that we have defined a cohort of extreme preterms and obtained ROP-treatment outcome for all of them. This study therefore can estimate the incidence of ROP treatment in this defined population and has identified a greatly increased risk of needing ROP treatment for babies born at 23 or 24 weeks, compared to babies born when more mature. There are no reports of ROP treatment rate by gestation from other UK centres but similar observations to ours have been made in other countries[9,10,11,12].

In conclusion, the recent increase in the incidence of ROP requiring treatment, which we have seen locally over our 7-year study period, appears to be at least in part due to the increased survival of premature infants. With on-going advances in neonatal intensive care facilities, particularly in developed countries, leading to the greater survival of extremely premature infants, it is likely that the incidence of ROP and ROP requiring treatment will continue to rise in future. With increasing centralisation of specialised services, the data we present may help capacity planning and service design for Eye Units involved with care of babies with ROP. The data will also help neonatologists and ophthalmologists when counselling the parents of babies born extremely preterm, about the likelihood of ROP developing which requires treatment.

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